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10/727,100	12/02/2003	Mark G. Erlander	022041-001410US	4395

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,100	ERLANDER ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,14,23,39 and 74-121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,14,23,39 and 74-121* is/are rejected.

7)☒ Claim(s) *74 and 102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 January 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 7, 14, 23, 39, 74-121 are pending in the application.

This Office Action is in response to the Amendment filed on 4/1/08.

Response to Amendment

The requirement for sequence compliance is considered satisfied in view of the deletion of the appendix.

Acknowledgement is made of the amendment of the specification and the objection is withdrawn.

The objection to drawing is maintained for reason set forth below.

The 112 2nd paragraph rejection applied to claims 10-11, 17-18, 23, 25, 29-33, 35, 39-40, 42, 43, 54-55, 58-63, 65 and 67 is moot because the claims are canceled.

The rejection of claims 7, 14, 23, 39, 74-121 under 35 U.S.C.112 1st paragraph is maintained for reasons set forth of the record mailed on 2/16/07 and further discussed below.

Claims 77 and 117 are rejected under 35 U.S.C. 112 2nd paragraph for reason discussed below.

Claims 74 and 102 are objected to for following reasons.

Drawings

The drawing submitted on 1/12/08 does not comply with the requirement because they do not contain all of the figures appears on the prior version of the sheet. Further, for drawing in Figures 3, 6 and 7, the vertical axis labeled with log2 does not clearly indicate what this axis represents. The horizontal axis is not labeled either. Although the graphs are explained in the specification, they still need to be labeled so that the

information represented by the graph may be clear. Otherwise, the numbers on the scale is meaningless.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 14, 23, 39, 74-121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is re-written to address the amendment of the claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

Claim 7 is drawn to a method to determine the risk of cancer recurrence in a subject afflicted with estrogen receptor (ER)+ breast cancer, said method comprising

determining an expected cancer recurrence for said subject by assaying a sample of breast cancer cells from said subject for a ratio of HoxB13 and IL17BR expression levels that is higher than the mean ratio of HoxB13 and IL17BR expression levels in breast cancer cells; or determine an expected lack of cancer recurrence for said subject by assaying a sample of breast cancer cells from said subject for a ratio of HoxB13 and IL17BR expression levels that is below the mean ratio of HoxB13 and IL17BR expression levels in breast cancer cells. Claim 14 is drawn to a method of determining the outcome of a subject having ER+ breast cancer, if said subject is treated with tamoxifen, by assaying a breast cancer sample from said subject wherein a ratio of HoxB13 and IL17BR expression levels that is below the mean ratio of HoxB13 and IL17BR expression in breast cancer cells indicates a cancer free outcome, and a ratio above the mean ratio of HoxB13 and IL17BR expression levels indicates an outcome comprising cancer recurrence. Claim 23 is drawn to a method to determine therapeutic treatment for an ER+ breast cancer patient based upon said patient's expected lack of response to tamoxifen treatment by determining lack of response to tamoxifen treatment for said patient by assaying a sample of breast cancer cells from said patient for a ratio of HoxB13 and IL17BR expression levels that is higher than the mean ratio of HoxB13 and IL17BR expression level in breast cancer cells; and selecting appropriate treatment for a patient where lack of responsiveness is indicated. Claims 39 is drawn to a method to determine risk of cancer recurrence in a human subject having ER+ breast cancer if treated with tamoxifen by assaying a sample of breast cells from said subject for increased expression of human HOXB13 sequences or decreased expression of IL17BR sequences, relative to the mean expression thereof in a breast cancer cells, as an indicator of tamoxifen non-

responsiveness, or decreased expression of human HoxB13 sequences, or increased or decreased expression of IL17BR sequences relative to the mean expression thereof in a breast cancer cell, as an indicator of tamoxifen responsiveness. Newly presented claims 118-120 are drawn to a method of determining the risk of cancer recurrence in a subject having ER+ breast cancer which has been or has not been treated with tamoxifen, or a method of determining lack of response to tamoxifen treatment, wherein an increased expression ratio of HoxB13 and IL17BR relative to the ratio in normal cells indicates cancer recurrence and lack of response to tamoxifen. Newly added claim 121 is drawn to a method to determine risk of cancer recurrence in a subject having ER+ breast cancer if treated with tamoxifen by assaying a sample of breast cancer cell for increased expression of HoxB13 sequences, relative to the expression to normal breast cells, wherein the increase in the expression indicates tamoxifen non-responsiveness. The dependent claims further limits the independent claims to specific sequences that are assayed, the regions where the transcript are assayed, the method of preparing breast cancer cell sample, the method of determining the expression of the transcript.

Breadth of the claims:

The claims are broad in that they encompass the determination of any outcome (14), cancer recurrence, choosing any appropriate therapeutic treatment for a subject having ER+ breast cancer, by measuring the ratio of expression of HoxB13 and IL17BR, or by either HoxB13 or IL17 BR alone. The broad breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/the existence of working examples:

The specification provides a number of HoxBI3 and ILI7BR sequences and teaches (by way of example) that any sequence, or unique portion thereof, of the ... ILI7RB sequence, identified by AF208111 or AF208111.1, may be used in the practice of the invention" and goes on to disclose the ILI7RB sequence of SEQ ID NO: 3 (see pages 28, lines 1-3 and SEQ ID NO:3 on page 28-29). Similarly, the specification teaches, also by way of example, that "any sequence encoding all or part of the protein encoded by any ILI7RB sequence disclosed herein may be used" (page 22, lines 15-18). In Example 1, the specification teaches that a 22,000-gene high-density oligonucleotide microarray was used to determine gene expression patterns from 62 ER+ breast cancer patients who were uniformly treated with tamoxifen (see page 55, lines 1-16). The ILI7BR and HOXBI3 oligonucleotide sequences used in the microarray are undisclosed. Thirty-three patients recurred while 29 patients remained disease free during a 14-year follow-up period (ibid). 149 genes were identified as correlative with tumor recurrence vs. non-recurrence, among them ILI7BR and HOXBI3 (see Table 1 on pages 55-59). The specification further discloses that samples from 60 ER+ breast cancer patients treated with adjuvant tamoxifen were selected based on treatment outcome and teaches that "28 had developed tumor recurrence with a median time of 4 years, and 32 remained disease-free with a median follow-up of 10 years (Table 3)" (pages 65-66, especially page 65, lines 5-8). The specification concedes that "patients who remained disease-free during the entire follow up period were likely to represent responders to TAM, although a small subset of them might have been cured by surgery alone" (page 65, lines 8-9). Statistical analysis on the gene expression differences among whole tissue sections from "responders" and "non-responders" yielded 19 genes with a p value at a cutoff of 0.001 (see page 7, lines 11-20

and Table 4 on pages 67-68). Again, HOXBI3 and ILI7BR were included among those identified (ibid). Gene expression patterns from laser capture microdissected (LCM) cells from the same patients were also tested (ibid). HOXBI3, ILI7BR, and CACNAID expression was found to be significantly correlative in both the LCM and whole tissue section samples (see page 70, lines 5-14). The specification further concedes that "[t]he significant correlations of CACNAID, HOXBI3 and ILI7BR with TAM treatment outcome suggest that these three genes may be novel predictors of TAM response" (page 70, lines 15116; emphasis added). Finally, in an effort to establish whether HOXBI3, ILI7BRI3, and CACNAID biomarkers could identify ER+, TAM responders and non-responders", Applicant performed receiver operating characteristic (ROC) analysis and multivariate analysis (see pages 70-74). The results, according to Applicant, "demonstrate that the three genes identified in this study were strong independent predictors of treatment outcome by adjuvant therapy independent of known clinicopathological parameters" (see paragraph bridging pages 73-74).

The specification discloses a number of sequences that are part of the human HoxB13 and IL17BR family and may be used in the claimed method. However, a review of all sequences reveals that each sequence is different from each other although they are given the same name. As stated above, the sequence identified in Table 4 is AF208111 and BC007092 for IL17BR and HoxB13 respectively. The specification does not demonstrate that the expression of the other sequences of the human HoxB13 and IL17BR family is correlated with responsiveness to tamoxifen treatment in ER+ breast cancer.

The specification does not teach what increases in HOXBI3 expression are required such that the increase is indicative of any given clinical outcome, even response to adjuvant tamoxifen therapy; nor does the specification teach how such an increase should be determined, i.e. whether the increase represents an increase within a patient's own sample over time or whether the standard upon which the "increase" is ascertained is based on some other standard. The same is true for the claimed increase or decrease in expression of ILI7BR. The amended claims now indicate that the increase or decrease is relative to the mean ratio of expression ratio in breast cancer cells. Applicants assert that the scaled mean value for responder and non-responder is represented by log2 value of 0 on the vertical axis, wherein the expression ratio of HoxB13 and IL17BR gene were set to a ratio wherein the mean value of 1 for each was set the mean ratio value. However, wherein the mean value for the expression level of each gene in Example 3 and 4 are determined from the population of breast cancer cells being analyzed from a number of patients (responder or non-responder), it is unclear how such value would be established from the claimed invention because the recitation of "mean ratio of HoxB13 and IL17BR expression levels in breast cancer cells" does not set forth where the reference set of breast cancer cell would come from. It is unclear whether it is a collection of cells from a large pool of breast cancer cells, or cells from the patient who is being tested prior to the treatment. Moreover, with regard to claims 118-121 which uses mean expression value from normal breast cells, the specification does not teach that the expression changes in the two recited gene in combination or alone can actually predict cancer recurrence, with or without tamoxifen treatment to the patient. The specification does not provide any statistical analysis of the expression level of HOXBI3 and ILI7BR sequences or even a

ratio of such expression levels for patients who were NOT treated with tamoxifen adjuvant therapy.

The specification does not teach how to use HOXBI3 and ILI7BR ratios, such that any prognosis of a subject with ER+ breast cancer can be determined and an appropriate treatment can be selected. Even the specification establishes a relationship between HoxB13 and IL17BR ratio is correlated responsiveness of breast cancer cells to adjuvant tamoxifen therapy in ER+ tumors, it does not teach what would be an appropriate treatment for a patient who does not respond to tamoxifen adjuvant therapy, except maybe not to use tamoxifen adjuvant therapy (for claims 23 and 120).

With regard to claim 39, the teaching of the specification actually contradicts the notion that decrease of IL17BR would indicate tamoxifen responsiveness (second part of the claim).

State of the prior art:

The literature does report an example of a gene expression profile which is predictive of a short interval of distant metastases" in breast cancer referred to as a ~poor prognosis" signature (van't Veer et al, *Nature* 415:530-536, 2002; IDS Ref BH; see entire document, especially the Abstract). This signature was derived from a test of 98 primary breast cancers from node-negative patients and consisted of 70 genes including those regulating cell cycle, invasion, metastasis and angiogenesis (ibid and page 530, 2nd column, 1st full paragraph), van't Veer et al also teach that, prior to their study, none of the signatures of breast cancer gene expression reported allowed for patient-tailored therapy strategies" (see page 530, 1st column, 1st paragraph). Moreover, Applicant

concedes in the specification that while estrogen receptor status is a powerful predictor of response to TAM (60% of ER+ tumors respond to TAM, whereas 10% of ER- tumors respond to the same treatment), "among ER+ tumors, no established predictors exist to identify the 40% non-responders" (page 70, lines 16-19). Thus, the state of the art is underdeveloped with respect to the use of a gene expression profiles generally (much less the use of only IL17BR and HOXB13 sequences) to predict breast cancer outcome.

Predictability of the art-Amount of experimentation necessary:

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu *(J. Pathol.*195(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of ~post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 -Discussion). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, page 20, Dec. 20, 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding

(left column, 3rd paragraph)- Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels. Chen et al *(Molecular and Cellular Proteomics* 1:304-313, 2002) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas- Only !7% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pages 311-312).

Most significantly, post-filing art does report the use of HOXBI3 and ILI7BR to attempt to predict clinical outcome in breast cancer patients treated with tamoxifen (Ma, et al. *Cancer Cell* 5:607-616, 2004; IDS Ref BI). This study also discloses a study in which gene expression profiles of ER+ primary breast Cancers treated with adjuvant tamoxifen therapy were generated (see entire document, especially the Abstract). However, Ma et al conclude that "It]he observation that a simple expression ratio of two genes, HOXBI3:ILI7BR, accurately predicts tumor recurrence in adjuvant tamoxifen-treated patient with early-stage ER-positive breast cancer is limited by the size of patient cohorts" and that it "will require confirmation in a large population-based cohort" (paragraph bridging pages 612-613). Moreover, Ma et al concede that "it remains to be

determined whether this two-gene ratio predicts a tumor's response to tamoxifen or its intrinsic aggressiveness, or both" and that a similarly case-matched cohort of untreated patients will be required to address this issue" (ibid). This level of unpredictability is exacerbated by the fact that "little is known about the relevance of HOXBI3 in breast cancer biology", and further that "[l]ittle information exists in the literature linking ILI7BR to breast cancer" as further taught by Ma, et al (page 611, 2nd column, 1st full paragraph and page 613, 1st column, 1st full paragraph).

Given the complex nature off invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. A skilled artisan would have to establish a number of things including that first, all HOXBI3 and ILI7BR sequences were predictive of clinical outcome in patients treated or not treated with tamoxifen, both alone and in combination (as a ratio); second, one of skilled in the art would then have to determine which levels of HOXBI3 and ILI7BR expression were indicative of any given clinical outcome/diagnosis/treatment course selection. Such testing is not routine and would require a burdensome and undue amount of trial-and-error experimentation.

Applicants assert that Jansen et al., and Jereval et al. and Goetz et al. recognizes the contribution of Ma et al., and only routine and repetitive experiment are needed as follow up to the teaching of Ma et al. Applicants are invited to provide a detailed explanation of how theses references enabled the claimed invention because the references do not fully address the lack of predictability as set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77 and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated from newly presented claim amendment.

Regarding claim 77, the word "derive" renders the claim indefinite because the nature and number of derivative process is unknown.

Claim 117 recites the limitation "said survival outcome" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 14 does not recite this term.

Claim Objections

Claims 74 and 102 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 already comprises the step of determining the expression level of HoxB13 and IL17BR, as such, claim 74 does not further limit claim 7. Similarly, claim 39 already recites a human subject, as such, claim 102 does not further limit claim 39.

This objection is necessitated from newly presented claim amendment.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636